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(54) **Coated microparticles with improved drug absorption**

Überzogene Mikropartikel mit verbesserter Arzneistoffabsorption

Microparticules enrobées avec une meilleure absorption du médicament

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Description

[0001] The present invention relates to a new method and compositions for improving the absorption of drugs taken by the oral route by means of encapsulation in millispheres of gellable hydrocolloids covered with positively charged polysaccharides.

BACKGROUND OF THE INVENTION

[0002] The oral route is preferred when administering drugs to all kinds of patients due to the advantages of this method relative to other routes which are more aggressive and/or more difficult to apply (intravenous, parenteral, subcutaneous...). Nevertheless, not all drugs are easily absorbed via the gastrointestinal tract. This absorption depends, among other factors, on the permeability of the gastrointestinal mucous membrane to the drug and on the acidic or enzymatic degratative processes to which the drug is subjected whilst it is inside the gastrointestinal tract. It is therefore clear that any factor which improves the speed of absorption of the drug or protects it from the above mentioned degradative processes will improve the clinical efficiency of that drug.

[0003] Recently a considerable amount of effort has been made to identify agents which are able to increase the permeability of the gastrointestinal mucous membrane to poorly absorbed products. Tensioactives (George, Sutter, Finegold, J. Infec. Dis. 136, 822 (1977), chelating agents (Cassidy, Tidball, J. Cell. Biol. 32, 672 (1967), salicylates (Higuchi, et al., U.S. Patent 4,462,991 (1984), anti-inflammatory agents (Yaginuma, et al., Chem. Pharm. Bull. 29 1974 (1961), phenothiazines (Alexander and Fix, U.S. Patent 4,425,357 (1984) acyl carnitines (Alexander and Fix, USSN 606, 054), fatty acids (Yamazaki, et al., J. Pharm. Pharmacol., 42, 441, (1990) have been described as able to increase gastrointestinal permeability to a large variety of compounds. Furthermore, considerable efforts have also been made to produce systems which protect drugs from the degradative gastrointestinal processes. Coverings of farinose (WO 89/11269), Polymers of lactic and glycolic acid (EP 0202159) and Calcium alginate (Chong-Kook K., Eun-Jin L., Int. J. Pharm., 79, 11, (1992), have been described as systems for administering drugs by the gastrointestinal route.

[0004] PCT WO 87/03197 describes microspheres which are less than 200 µm in size and which are obtained from a drug and a material that has ionic exchange properties, such as diethylaminoethyl-dextran.

[0005] PCT WO 88/09163, WO 89/03207, WO 91/02545 and WO 91/06282 describe microspheres which are less than 200 µm in size and whose centres are made of starch, starch derivatives, gelatine, albumen, collagen, dextran or dextran derivatives and which can optionally be covered by polymers such as alginates or diethylaminoethyldextrans among others. The use of such microspheres is always described with reference to application by routes other than the oral route and they can optionally be provided with absorption promoters such as lysolecithins or alginates.

[0006] EP 391803 describes an industrial procedure for obtaining capsules of alginates in a continuous process by a procedure which is itself described in previous literature (Grant, G.I., et al.; FEBS Lett. 32, 195 (1973).

[0007] PCT WO 92/00732 describes pellets of polysaccharides (in particular pectins) which are able to form coacervates with polyvalent cations, containing a drug and covered again by the same type of polysaccharide. These particles are administered by the oral route, the drug being liberated in the colon after the polysaccharide covering has been dissolved by bacteria.

BRIEF DESCRIPTION OF THE INVENTION

[0008] The presence of a certain negative charge density on the surface of most gastrointestinal mucous membranes is known, and the authors therefore directed their research towards obtaining a system of administering drugs by the oral route consisting of millispheres with a certain degree of positive surface charge (covered with cationic polysaccharides) in order to achieve a bioadhesive effect on the surface of the gastrointestinal mucous membranes.

[0009] As a result of this research it was discovered, surprisingly, that when drugs which are difficult to absorb gastrointestinally are administered by the oral route incorporated inside millicapsules of gellable hydrocolloids reticulated with cationic polysaccharides, there is a marked increase in the bioavailability of said drugs, and that this increase in the bioavailability of the encapsulated drug relative to the bioavailability of the free drug is even greater if promoters of absorption via the mucous membranes are encapsulated together with the drug.

[0010] Therefore, one object of the present invention is to improve the bioavailability of drugs which are difficult to absorb when administered by the oral route by means of encapsulating the drugs inside matrices of gellable hydrocolloids whose surfaces are covered by cationic polysaccharides, optionally incorporating together with the drug products which are able to modify the permeability of the gastrointestinal mucous membranes to the drug which is encapsulated.

[0011] A further object of the present invention is a new system of administering drugs by the oral route consisting of millispheres, microspheres, nanospheres or array-type particles of salts of gellable hydrocolloids whose surfaces are covered by cationic polysaccharides, and incorporating a pharmacologically active drug.

[0012] A further object of the present invention is a new system of administering drugs by the oral route, consisting

of millispheres, microspheres, nanospheres or array-type particles of salts of gellable hydrocolloids whose surfaces are covered by cationic polysaccharides, and incorporating a pharmacologically active drug together with one or several promoters of absorption via the mucous membranes.

[0013] A further object of the present invention is a new system of administering drugs by the oral route, consisting of millispheres, microspheres, nanospheres or array-type particles of salts of gellable hydrocolloids whose surfaces are covered by cationic polysaccharides, and incorporating a pharmacologically active drug wherein optionally, and in particular in the case of drugs which are sensitive to the chemical/enzymatic conditions of the stomach, said particles are administered inside capsules of gelatine with an enteric covering which protects the particles until they enter the duodenum.

[0014] These formulations have the inherent advantages of the oral route compared with other routes for administering drugs, i.e. they are easier to administer, more comfortable, less aggressive and safer for the patient.

[0015] Furthermore, the formulations claimed have the advantage of enabling the drugs incorporated to reach the circulatory system without being destroyed during their passage through the digestive tract, in addition providing a high degree of bioavailability of the drug administered.

DETAILED DESCRIPTION OF THE INVENTION

[0016] The present invention comprises the preparation and use in a pharmaceutical preparation of dehydrated millispheres, microspheres, nanospheres or array-type particles consisting of a nucleus or matrix of a gellable hydrocolloid onto which has been deposited a film of a cationic polysaccharide, the matrix of gellable hydrocolloid being able to incorporate one or several pharmacologically active drugs, and where optionally it is possible to incorporate together with the drug or drugs one or several promoters of absorption via the mucous membranes.

[0017] The incorporation of the drug inside the matrix of gellable hydrocolloid can be carried out principally in the following two ways:

1) - The drug is dissolved in the solution of the gellable hydrocolloid prior to the gelling thereof.

2) - The drug is incorporated by diffusion towards the hydrocolloid matrix from a concentrated solution of the drug, after the gelling of the matrix and before covering with the cationic polysaccharide.

[0018] Before continuing with the description of the present invention, reference is made to the accompanying drawings which are included in order that the invention may be better understood. In the drawings:

[0019] Figure 1 represents a millisphere consisting of a matrix of a gellable hydrocolloid which contains the drug and onto which has been deposited a covering film of a cationic saccharide, according to the present invention.

[0020] Figures 2 and 3 are flow diagrams of the method of incorporating the drug inside the matrix of gellable hydrocolloid by means of dissolving the drug in the solution of the gellable hydrocolloid prior to the gelling thereof.

[0021] Figures 4 and 5 are flow diagrams of the method of incorporating the drug inside the matrix of gellable hydrocolloid by the diffusion of the drug towards the matrix from a concentrated solution of the drug, after the gelling of the matrix and before covering with the cationic polysaccharide.

[0022] Gellable hydrocolloids is taken to refer to all polymers of biological or synthetic origin which are soluble in water and which can form solid gels by the cooling of their aqueous solutions, by interaction with the salts of metallic elements (more particularly the salts of alkaline-earth metals and more particularly calcium salts), by variations in the pH of their aqueous solutions, or by chemical reticulation. More particularly, gellable hydrocolloids is taken to refer to the following biopolymers: agar, pectin, xanthane gum, guar gum, locust bean gum, hyaluronic acid, casein and their mixtures, and even more particularly gellable hydrocolloids is taken to refer to the following biopolymers: water-soluble salts of alginic acid (more particularly sodium alginate), carrageenates and their mixtures.

[0023] Cationic polysaccharide is taken to refer to natural polysugars chemically functionalized with residues which can support a positive charge. More particularly cationic polysaccharides is taken to refer to the amino-polysugars and their acid salts, more particularly dextrans functionalized with primary, secondary, tertiary and/or quaternary amine groups, and even more particularly diethylaminoethyl-dextran and dimethylaminoethyl-dextran and their acid salts.

[0024] Promoters of absorption via the mucous membranes is taken to refer to all compounds capable of increasing the bioavailability of a drug when administered together with the drug by application to the nasal, gastrointestinal or vaginal mucous membranes or by the transdermic route. More particularly absorption promoters is taken to refer to the following groups of compounds:

- Esters of choline
- Chelating agents
- Salicylates
- Phenothiazines

- Acyl carnitins
- Alpha-cetoaldehydes
- Tensioactives
- Collates
- Lysolecithins

[0025] More particularly absorption promoters is taken to refer to lysolecithin and to the salts of fatty acids, in particular sodium caproate (sodium hexanoate), sodium caprylate (sodium octanoate), sodium caprate (sodium decanoate) and sodium laurate (sodium dodecanoate).

[0026] The drugs which can be incorporated in the new system for administering drugs which forms the object of the present invention include, but are not limited to, the following:

- Anti-bacterial drugs such as gentamycin; quinolones such as ciprofloxacin; penicillins or cephalosporins.
- Anti-viral agents such as rifampicin or acyclovir.
- Anti-fungal compounds such as anphoterecin B, myconazole, terconazole, econazole, isoconazole, thioconazole, biphonazole, clotrimazole, ketoconazole, butaconazole, itraconazole, oxiconazole, phenticonazole, nystatin, naphthyphene, zinoconazole, cyclopyroxolamine or fluconazole.
- Anti-parasitic compounds such as derivatives of antimony.
- Anti-tumoral and anti-neoplastic compounds such as adriamycin, vinblastine, vincristine, mitomycin C, doxorubicin, daunorubicin, methotrexate, cisplatin and others.
- Anti-metabolites.
- Proteins such as albumen.
- Toxins such as diphtheric toxin.
- Enzymes such as catalase.
- Peptides such as hirudin, somatostatin or timopentin.
- Hormones such as oestrogen.
- Peptide hormones such as human growth hormone, porcine growth hormone, bovine growth hormone, human calcitonin, salmon calcitonin, carbocalcitonin, insulin or LHRH and analogues.
- Hormonal antagonists.
- Neurotransmitters such as acetylcholine.
- Neurotransmitter antagonists.
- Glycoproteins such as hyaluronic acid.
- Lipoproteins such as alpha-lipoprotein.
- Immunoglobulins such as IgG.
- Immunomodulators such as interferon or interleukin.
- Immunosuppressors such as cyclosporin-A.
- Vasodilators.
- Colourings such as Arsenaze III.
- Radioactive labellers such as ^{14}C.
- Radio-opaque compounds such aS ^{90}Te.
- Fluorescent compounds such as carboxy-fluorescein.
- Cellular receptors such as oestrogen receptor protein.
- Non-steroidal anti-inflammatory agents such as indomethacin, ibuprofen, sulindac, diclofenac, ketorolac or naproxen.
- Anti-inflammatory agents such as dexametasone.
- Anti-glaucomatous agents such as pilocarpine or thymolol.
- Mydriatic compounds.
- Local anaesthetics such as lidocaine.
- Narcotics such as codeine.
- Vitamins such as alpha-tocopherol.
- Nucleic acids such as thymine.
- Polynucleotides such as RNA.
- Psychoactive or anxiolytic compounds such as diazepam.
- Mono-, di- and poly-saccharides such as glycogen.
- Glycosaminoglycanes such as non-fractionated heparins, heparins of low molecular weight, pentasaccharide, dermatan sulphate and its derivatives, heparan sulphate and its derivatives, chondroitin-4-sulphate or chondroitin-6-sulphate and its derivatives.
- Cardiovascular agents such as alpha-blockers, beta-blockers, calcium channel blockers, ACE inhibitors, histamine

H2 receptor inhibitors or serotonin H3T receptor inhibitors.

- Prostaglandins.

[0027] Optionally, and in particular in the case of drugs which are sensitive to the chemical/enzymatic conditions of the stomach, said particles are administered inside capsules of gelatine with an enteric covering which protects the particles until they enter the duodenum.

[0028] The invention is illustrated below by means of the following non-limiting examples of the scope of said invention.

[0029] EXAMPLE 1: Obtaining capsules of calcium alginate covered with DEAE-Dextran incorporating sodium heparin of low molecular weight (SLMWH).

[0030] 500 mg of SLMWH (4 kDaltons) are dissolved in 10 ml of 1% sodium alginate solution by shaking gently. The resulting solution is added drop by drop through a 0.8 mm hole to 40 ml of a gently shaken 0.25 M solution of $CaCl_2$ in H_2O. Once the addition of the millispheres is complete they are kept in the bulk of the shaken $CaCl_2$ solution for 10 minutes, after which time the balls are separated by filtering and washed with 25 ml of deionized H_2O.

[0031] The spheres of calcium alginate thus formed are resuspended in 20 ml of an 8% solution of diethylaminoethyl-dextran hydrochloride (Mr = 500000) in H_2O, keeping the system gently shaken for 30 minutes.

[0032] The spheres are separated by filtering, washed twice with 20 ml of deionized H_2O and dried.

[0033] EXAMPLE 2: Obtaining capsules of calcium alginate covered with DEAE-dextran incorporating sodium heparin of low molecular weight (SLMWH) and sodium caprate.

[0034] 500 mg of SLMWH (4 kDaltons) and 200 mg of sodium caprate are dissolved in 10 ml of 1% sodium alginate solution by shaking gently. The resulting solution is added drop by drop through a 0.8 mm hole to 40 ml of a gently shaken 0.25 M solution of $CaCl_2$ in H_2O. Once the addition of the millispheres is complete they are kept in the bulk of the shaken $CaCl_2$ solution for 10 minutes, after which time the balls are separated by filtering and washed with 25 ml of deionized H_2O.

[0035] The spheres of calcium alginate thus formed are re-suspended in 20 ml of an 8% solution of diethylaminoethyl-dextran hydrochloride (Mr = 500000) in H_2O, keeping the system gently shaken for 30 minutes.

[0036] The spheres are separated by filtering, washed twice with 20 ml of deionized H_2O and dried.

[0037] EXAMPLE 3: Obtaining capsules of calcium alginate covered with DEAE-Dextran incorporating sodium heparin of low molecular weight (SLMWH). Method of encapsulation by diffusion.

[0038] 10 ml of 1% sodium alginate solution are added through a 0.8 mm hole to 40 ml of a 0.25 M solution of $CaCl_2$. The system is kept shaken for 10 minutes.

[0039] The spheres formed are separated by filtering and washed with 25 ml of deionized H_2O, after which they are re-suspended in a solution of heparin, with a concentration of 100 mg/ml, and kept in the bulk of said solution and gently shaken for a period of 6 hours to allow the drug to diffuse inside the capsules. The capsules are then separated by filtering and washed three times with 25 ml of H_2O.

[0040] The spheres of calcium alginate incorporating SLMWH thus formed are re-suspended in 20 ml of an 8% solution of diethylaminoethyl-dextran hydrochloride (Mr = 500000) in H_2O, keeping the system gently shaken for 30 minutes.

[0041] The spheres are separated by filtering, washed twice with 20 ml of deionized H_2O and dried.

[0042] EXAMPLE 4: Obtaining capsules of calcium alginate covered with DEAE-Dextran incorporating sodium heparin of low molecular weight (SLMWH) and sodium caprate. Method of encapsulation by diffusion.

[0043] 10 ml of 1% sodium alginate solution containing 2% sodium caprate are added through a 0.8 mm hole to 40 ml of a 0.25 M solution of $CaCl_2$. The system is kept shaken for 10 minutes.

[0044] The spheres formed are separated by filtering and washed with 25 ml of deionized water, after which they are re-suspended in a solution of heparin, with a concentration of 150 mg/ml, and kept in the bulk of said solution and gently shaken for a period of 6 hours to allow the drug to diffuse inside the capsules. The capsules are then separated by filtering and washed three times with 25 ml of H_2O.

[0045] The spheres of calcium alginate incorporating SLMWH thus formed are re-suspended in 20 ml of an 8% solution of diethylaminoethyl-dextran hydrochloride (Mr = 500000) in H_2O, keeping the system gently shaken for 30 minutes.

[0046] The spheres are separated by filtering, washed twice with 20 ml of deionized H_2O and dried.

[0047] EXAMPLE 5: Bioavailability tests on the capsules prepared according to examples 1 and 2.

- Design:
  Bioavailability studies in which the animals received 40 mg of heparin by the oral route or 10 mg by the subcutaneous route over a period of three days.
- Animals:
  Four dogs (2 for each treatment), each approximately 15 kg in weight.
- Measurements:
  A bioassay (anti-Xa activity) was used to measure the concentrations in the plasma.

The anti-Xa activity in the plasma was measured ex-vivo using a chromogenic test using a commercially available kit (Coatest) and expressed in IU/ml. The values were calculated from a calibration curve obtained in-vitro by adding different quantities of SLMWH to dog plasma.

The blood was extracted from the femoral vein. Starting on the second day of experiments samples were collected before and 1, 2, 3, 4 and 6 hours after oral or subcutaneous administration, sodium citrate was added to the samples (9 vol. sangre : 1 vol. 3.8% sodium citrate) followed by centrifuging at 1200 rpm for 20 minutes at 4°C. The plasma was separated immediately and the anti-Xa activity was tested.

The urine samples were treated with chondroitinase AC to eliminate the endogenous chondroitins. The residue was analyzed by means of proton NMR and HPLC (to determine the molecular weight).

- Results:

Even on the second day of experiments, the levels of heparin in the blood as a result of administering SLMWH in the form of capsules by the oral route, or injected subcutaneously, were detectable using the anti-Xa activity method.

[0048] Comparable peak values (0.2 - 0.4 IU/ml) were found after subcutaneous or oral administration, as well as a significant continued activity (> 0.1 IU/ml) for 3 hours only after subcutaneous administration.

[0049] On the third day of experiments the basal values of anti-Xa activity before the final dose were significantly higher than the corresponding values on the previous day.

[0050] Peak values (0.8 - 1.2 IU/ml) were found 1 and 2 hours after oral and subcutaneous administration as well as a significant activity (> 0.3 IU/ml) after 6 hours in the case of both treatments.

[0051] The urine analyses gave the following results:

[0052] The H_1-NMR test detected the presence of partially disulphated heparin.

[0053] The HPLC test indicated a molecular weight of 5 kDaltons.

[0054] EXAMPLE 6: Incorporation procedures for several drugs

DRUG	GELLABLE HYDROCOLLOID	CATIONIC POLYSACCHARIDE	ABSORPTION PROMOTER	METHOD OF INCORPORATING THE DRUG
ACYCLOVIR	Sodium alginate	DEAE-Dextran	Lysolecithin	Example N°2
ACYCLOVIR HYDROCHLORIDE	Carrageenate	DEAE-Dextran		Example N°3
CYCLOSPORIN	Sodium alginate	DEAE-Dextran	Sodium caprate	Example N°2
CYCLOSPORIN	Sodium alginate	DEAE-Dextran		Example N°1
CALCITONIN	Sodium alginate	DEAE-Dextran	Lysolecithin	Example N°2
CARBOCALCITONIN	Sodium alginate	DEAE-Dextran	Sodium caprate	Example N°2
INSULIN	Sodium alginate	DEAE-Dextran	Sodium caprate	Example N°2
ERYTHROMYCIN	Sodium alginate	DEAE-Dextran	Sodium caprate	Example N°1
NIMODIPIN	Sodium alginate	DEAE-Dextran		Example N°2
FLUCONAZOLE	Sodium alginate	DEAE-Dextran	Sodium caprate	Example N°2
CYPROFLOXACIN	Sodium alginate	DEAE-Dextran	Sodium caprate	Example N°4
FAMOTIDIN	Sodium alginate	DEAE-Dextran	Sodium caprate	Example N°2
KETOROLAC	Sodium alginate	DEAE-Dextran	Lysolecithin	Example N°4
THROMETAMIN DICLOFENAC	Sodium alginate	DEAE-Dextran		Example N°2

Claims

1. A pharmaceutical preparation, characterized in that consists of dehydrated millispheres, dehydrated microspheres,

dehydrated nanospheres or array-type dehydrated particles consisting of a nucleus of a gellable hydrocolloid onto which has been deposited a film of a cationic polysaccharide, and incorporating inside a pharmacologically useful drug.

2. A pharmaceutical preparation according to claim 1, characterized in that optionally said nucleus also incorporates a promoter of absorption via the mucous membranes.

3. A pharmaceutical preparation according to claims 1 and 2, characterized in that the gellable hydrocolloids are polymers of biological or synthetic origin which are soluble in water and which can form solid gels by the interaction with the salts of metallic elements (more particularly the salts of alkaline-earth metals and more particularly calcium salts) or by variations in the pH of their aqueous solutions or by chemical reticulation.

4. A pharmaceutical preparation according to claims 1, 2 and 3, characterized in that the gellable hydrocolloids are preferably agar, pectin, xanthane gum, guar gum, locust bean gum, hyaluronic acid, casein, water-soluble salts of alginic acid (more particularly sodium alginate), and their mixtures.

5. A pharmaceutical preparation according to claims 1 and 2, characterized in that the cationic polysaccharides are natural polysugars with residues which can support a positive charge and natural polysugars chemically functionalized with residues which can support a positive charge, in particular the amino-polysugars and their acid salts; dextrans functionalized with primary, secondary, tertiary and/or quaternary amine groups and their acid salts.

6. A pharmaceutical preparation according to claims 1, 2 and 5, characterized in that the cationic polysaccharides are preferably diethylaminoethyl-dextran and dimethylaminoethyl-dextran, their acid salts and their mixtures.

7. A pharmaceutical preparation according to claims 1 and 2, characterized in that the promoters of absorption via the mucous membranes are esters of choline, chelating agents, salicylates, phenothiazines, acyl carnitines, alpha-cetoaldehydes, tensioactives, collates, lysolecithins and their mixtures.

8. A pharmaceutical preparation according to claims 1, 2 and 7, characterized in that the promoters of absorption via the mucous membranes are preferably lysolecithin and salts of fatty acids, in particular sodium caproate (sodium hexanoate), sodium caprylate (sodium octanoate), sodium caprate (sodium decanoate) and sodium laurate (sodium dodecanoate).

9. A pharmaceutical preparation according to claims 1 and 2, characterized in that the drugs incorporated are:

- Anti-bacterial drugs such as gentamycin; quinolones such as ciprofloxacin; penicillins or cephalosporins;
- Anti-viral agents such as rifampicin or acyclovir;
- Anti-fungal compounds*such as anphoterecin B, myconazole, terconazole, econazole, isoconazole, thioconazole, biphonazole, clotrimazole, ketoconazole, butaconazole, itraconazole, oxiconazole, phenticonazole, nystatin, naphthyphene, zinoconazole, cyclopyroxolamine or fluconazole;
- Anti-parasitic compounds such as derivatives of antimony;
- Anti-tumoral and anti-neoplastic compounds such as adriamycin, vinblastine, vincristine, mitomycin C, doxorubicin, daunorubicin, methotrexate, cisplatin and others;
- Anti-metabolites;
- Proteins such as albumen;
- Toxins such as diphtheric toxin;
- Enzymes such as catalase;
- Peptides such as hirudin, somatostatin or timopentin;
- Hormones such as oestrogen;
- Peptide hormones such as human growth hormone, porcine growth hormone, bovine growth hormone, human calcitonin, salmon calcitonin, carbocalcitonin, insulin or LHRH and analogues;
- Hormonal antagonists;
- Neurotransmitters such as acetylcholine;
- Neurotransmitter antagonists;
- Glycoproteins such as hyaluronic acid;
- Lipoproteins such as alpha-lipoprotein;
- Immunoglobulins such as IgG;
- Immunomodulators such as interferon or interleukin;

- Immunosuppressors such as cyclosporin-A;
- Vasodilators;
- Colourings such as Arsenaze III;
- Radioactive labellers such as ^{14}C;
- Radio-opaque compounds such as ^{90}Te;
- Fluorescent compounds such as carboxy-fluorescein;
- Cellular receptors such as oestrogen receptor protein;
- Non-steroidal anti-inflammatory agents such as indomethacin, ibuprofen, sulindac, diclofenac, ketorolac or naproxen;
- Anti-inflammatory agents such as dexametasone;
- Anti-glaucomatous agents such as pilocarpine or thymolol;
- Mydriatic compounds;
- Local anaesthetics such as lidocaine;
- Narcotics such as codeine;
- Vitamins such as alpha-tocopherol;
- Nucleic acids such as thymine;
- Polynucleotides such as RNA;
- Psychoactive or anxiolytic compounds such as diazepam;
- Mono-, di- and poly-saccharides such as glycogen;
- Glycosaminoglycanes such as non-fractionated heparins, heparins of low molecular weight, pentasaccharide, dermatan sulphate and its derivatives, heparan sulphate and its derivatives, chondroitin-4-sulphate or chondroitin-6-sulphate and its derivatives;
- Cardiovascular agents such as alpha-blockers, beta-blockers, calcium channel blockers, ACE inhibitors, histamine H2 receptor inhibitors or serotonin H3T receptor inhibitors;
- Prostaglandins.

10. A procedure for obtaining the pharmaceutical preparation according to claim 1, characterized in that the drug is dissolved, suspended or emulsified in a solution of the gellable hydrocolloid; the resulting solution, suspension or emulsion is added to a medium in which the gelling of the hydrocolloid takes place (gelling solution); the millispheres, microspheres, nanospheres or array-type particles which are formed are separated and suspended in a solution of the cationic polysaccharide where the deposition of the cationic polysaccharide onto the surface of the spheres takes place, after which the covered spheres are separated, washed and dried.

11. A procedure for obtaining the pharmaceutical preparation according to claims 1 and 2, characterized in that the drug and the absorption promoter are dissolved, suspended or emulsified in a solution of the gellable hydrocolloid solution; the resulting solution, suspension or emulsion is added to a medium in which the gelling of the hydrocolloid takes place (gelling solution); the millispheres, microspheres, nanospheres or array-type particles which are formed are separated and suspended in a solution of the cationic polysaccharide where the deposition of the cationic polysaccharide onto the surface of the spheres takes place, after which the covered spheres are separated, washed and dried.

12. A procedure for obtaining the pharmaceutical preparation according to claim 1, characterized in that the absorption promoter is dissolved, suspended or emulsified in a solution of the gellable hydrocolloid; the resulting solution, suspension or emulsion is added to a medium in which the gelling of the hydrocolloid takes place (gelling solution); the millispheres, microspheres, nanospheres or array-type particles which are formed are separated and suspended in a concentrated solution of the drug from which the drug diffuses inside the spheres; then the millispheres, microspheres, nanospheres or array-type particles are separated and suspended in a solution of the cationic polysaccharide where the deposition of the cationic polysaccharide onto the surface of the spheres takes place, after which the covered spheres are separated, washed and dried.

13. A procedure for obtaining the pharmaceutical preparation according to claim 1, characterized in that the solution of the gellable hydrocolloid is added to a medium in which the gelling of the hydrocolloid takes place (gelling solution); the millispheres, microspheres, nanospheres or array-type particles which are formed are separated and suspended in a concentrated solution of the drug from which the drug diffuses inside the spheres; then the millispheres, microspheres, nanospheres or array-type particles are separated and suspended in a solution of the cationic polysaccharide where the deposition of the cationic polysaccharide onto the surface of the spheres takes place, after which the covered spheres are separated, washed and dried.

14. A pharmaceutical preparation according to claims 1 to 9, characterized in that optionally, and in particular in the case of drugs which are sensitive to the chemical/enzymatic conditions of the stomach, said particles are administered inside capsules of gelatine with an enteric covering which protects the particles until they enter the duodenum.

Patentansprüche

1. Pharmazeutisches Präparat, dadurch gekennzeichnet, daß es dehydratisierte Milliкügelchen, dehydratisierte Mikroкügelchen, dehydratisierte Nanoкügelchen oder dehydratisierte Teilchen vom Array-Typ umfaßt, die aus einem Kern aus einem gelierfähigen Hydrokolloid bestehen, auf den ein Film aus einem kationischen Polysaccharid abgeschieden wurde, wobei im Inneren ein pharmazeutisch nützliches Arzneimittel enthalten ist.

2. Pharmazeutisches Präparat nach Anspruch 1, dadurch gekennzeichnet, daß der Kern gegebenenfalls auch einen Promotor für die Absorption über die Schleimhäute enthält.

3. Pharmazeutisches Präparat nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die gelierfähigen Hydrokolloide Polymere biologischen oder synthetischen Ursprungs sind, die in Wasser löslich sind und durch Wechselwirkung mit den Salzen von Metallelementen, insbesondere mit den Salzen von Erdalkalimetallen, vor allem mit Calciumsalzen, oder durch Variationen des pH-Werts ihrer wäßrigen Lösungen oder durch chemische Vernetzung feste Gele bilden können.

4. Pharmazeutisches Präparat nach Anspuch 1, 2 und 3, dadurch gekennzeichnet, daß die gelierfähigen Hydrokolloide vorzugsweise Agar, Pektin, Xanthangummi, Guargummi, Johannisbrotgummi, Hyaluronsäure, Casein, wasserlösliche Salze von Alginsäure, insbesondere Natriumalginat, und Gemische davon sind.

5. Pharmazeutisches Präparat nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die kationischen Polysaccharide folgende sind: natürliche Polysaccharide mit Resten, die eine positive Ladung tragen können, und natürliche Polysaccharide, die mit Resten, die eine positive Ladung tragen können, chemisch funktionalisiert sind, insbesondere die Aminopolysaccharide und deren Säuresalze; Dextrane, die mit primären, sekundären, tertiären und/oder quaternären Aminogruppen funktionalisiert sind, und deren Säuresalze.

6. Pharmazeutiches Präparat nach einem der Ansprüche 1, 2 und 5, dadurch gekennzeichnet, daß die kationischen Polysaccharide vorzugsweise Diethylaminoethyldextran und Dimethylaminoethyldextran, deren Säuresalze und Gemische davon sind.

7. Pharmazeutisches Präparat nach einem der Ansprüche 1 und 2, dadurch gekennzeichnet, daß die Promotor für die Absorption über die Schleimhäute Ester von Cholin, Chelatbildner, Salicylate, Phenothiazine, Acylcarnitine, α-Ketoaldehyde, Tensioaktive, Collate, Lysolecithine und Gemische davon sind.

8. Pharmazeutisches Präparat nach einem der Ansprüche 1, 2 und 7, dadurch gekennzeichnet, daß die Promotor für die Absorption über die Schleimhäute vorzugsweise Lysolecithin und Salze von Fettsäuren sind, insbesondere Natriumcapronat (Natriumhexanat), Natriumcaprylat (Natriumoctanat), Natriumcaprinat (Natriumdecanat) und Natriumlaurat (Natriumdodecanat).

9. Pharmazeutisches Präparat nach einem der Ansprüche 1 und 2, worin die enthaltenen Arzneimittel folgende sind:

- Antibakterielle Arzneimittel, wie z.B. Gentamycin; Chinolone, wie z.B. Ciprofloxacin; Penicilline oder Cephalosporine;
- Antivirale Mittel, wie z.B. Rifampicin oder Acyclovir;
- Antifungale Verbindungen, wie z.B. Anphoterecin B, Myconazol, Terconazol, Econazol, Isoconazol, Thioconazol, Biphonazol, Clotrimazol, Ketoconazol, Butaconazol, Itraconazol, Oxiconazol, Phenticonazol, Nystatin, Naphtyphen, Zinoconazol, Cyclopyroxolamin oder Fluconazol;
- Antiparasitäre Verbindungen, wie z.B. Derivate von Antimon;
- Antitumor- und Antineoplastie-Verbindungen, wie z.B. Adriamycin, Vinblastin, Vincristin, Mitomycin C, Doxorubicin, Daunorubicin, Methotrexat, Cisplatin u.a.;
- Antimetaboliten;
- Proteine, wie z.B Albumin;
- Toxine, wie z.B. Diphterietoxin;

- Enzyme, wie z.B. Catalase;
- Peptide, wie z.B. Hirudin, Somatostatin oder Timopentin;
- Hormone, wie z.B. Östrogen;
- Peptidhormone, wie z.B. menschliches Wachstumshormon, Schweinewachstumshormon, Rinderwachstumshormon, menschliches Calcitonin, Lachs-Calcitonin, Carbocalcitonin, Insulin oder LHRH und Analoge;
- Hormon-Antagonisten;
- Neurotransmitter, wie z.B. Acetylcholin;
- Neurotransmitter-Antagonisten;
- Glykoproteine, wie z.B. Hyaluronsäure;
- Lipoproteine, wie z.B. α-Lipoprotein;
- Immunglobuline, wie z.B. IgG;
- Immunmodulatoren, wie z.B. Interferon oder Interleukin;
- Immunsuppressoren, wie z.B. Cyclosporin A;
- Vasodilatatoren;
- Farbstoffe, wie z.B. Arsenaze III;
- Radioaktive Marker, wie z.B. ^{14}C;
- Strahlenundurchlässige Verbindungen, wie z.B. ^{90}Te;
- Fluoreszenzverbindungen, wie z.B. Carboxyfluorescein;
- Zell-Rezeptoren, wie z.B. Östrogen-Rezeptorprotein;
- entzündungshemmende Nichtsteroid-Mittel, wie z.B. Indomethacin, Ibuprofen, Sulindac, Diclofenac, Ketorolac oder Naproxen;
- Entzündungshemmende Mittel, wie z.B. Dexametason;
- Antiglaukomatöse Mittel, wie z.B. Pilocarpin oder Thymolol;
- Mydriatische Verbindungen;
- Lokalanästhetika, wie z.B. Lidocain;
- Narkotika, wie z.B. Codein;
- Vitamine, wie z.B. α-Tocopherol;
- Nukleinsäuren, wie z.B. Thymin;
- Polynukleotide, wie z.B. RNA;
- Psychoaktive oder anxiolytische Verbindungen, wie z.B. Diazepam;
- Mono-, Di- und Polysaccharide, wie z.B. Glykogen;
- Glykosaminoglykane, wie z.B. nichtfraktionierte Heparine, niedermolekulare Heparine, Pentasaccharid, Dermatansulfat und dessen Derivate, Heparansulfat und dessen Derivate, Chondroitin-4-sulfat oder Chondoitin-6-sulfat und dessen Derivate;
- Kardiovaskuläre Mittel, wie z.B. Alphablocker, Betablocker, Calciumkanalblocker, ACE-Hemmer, Histamin-H2-Rezeptor-Inhibitoren oder Serotonin-H3T-Rezeptor-Inhibitoren;
- Prostaglandine.

10. Verfahren zum Erhalten des pharmazeutischen Präparats nach Anspruch 1, dadurch gekennzeichnet, daß das Arzneimittel in einer Lösung des gelierfähigen Hydrokolloids gelöst, suspendiert oder emulgiert wird; die resultierende Lösung, Suspension oder Emulsion einem Medium zugesetzt wird, in dem Gelieren des Hydrokolloids erfolgt (Gelierlösung); die gebildeten Millikügelchen, Mikrokügelchen, Nanokügelchen oder Teilchen vom Array-Typ abgetrennt und in einer Lösung des kationischen Polysaccharids suspendiert werden, wo die Ablagerung des kationischen Polysaccharids auf der Oberfläche der Kügelchen erfolgt; wonach die beschichteten Kügelchen abgetrennt, gewaschen und getrocknet werden.

11. Verfahren zum Erhalten des pharmazeutischen Präparats nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß das Arzneimittel und der Absorptionsaktivator in einer Lösung der gelierfähigen Hydrokolloid-Lösung gelöst, suspendiert oder emulgiert werden; die resultierende Lösung, Suspension oder Emulsion einem Medium zugesetzt wird, in dem Gelieren des Hydrokolloids erfolgt (Gelierlösung); die gebildeten Millikügelchen, Mikrokügelchen, Nanokügelchen oder Teilchen vom Array-Typ abgetrennt und in einer Lösung des kationischen Polysaccharids suspendiert werden, wo die Ablagerung des kationischen Polysaccharids auf der Oberfläche der Kügelchen erfolgt; wonach die beschichteten Kügelchen abgetrennt, gewaschen und getrocknet werden.

12. Verfahren zum Erhalten des pharmazeutischen Präparats nach Anspruch 1, dadurch gekennzeichnet, daß der Absorptionspromotor in einer Lösung der gelierfähigen Hydrokolloids gelöst, suspendiert oder emulgiert wird; die resultierende Lösung, Suspension oder Emulsion einem Medium zugesetzt wird, in dem Gelieren des Hydrokolloids erfolgt (Gelierlösung); die gebildeten Millikügelchen, Mikrokügelchen, Nanokügelchen oder Teilchen vom Array-

Typ abgetrennt und in einer konzentrierten Lösung des Arzneimittels suspendiert werden, aus der das Arzneimittel in die Kügelchen eindiffundiert; wonach die Millikügelchen, Mikrokügelchen, Nanokügelchen oder Teilchen vom Array-Typ abgetrennt und in einer Lösung des kationischen Polysaccharids suspendiert werden, wo die Ablagerung des kationischen Polysaccharids auf der Oberfläche der Kügelchen erfolgt; wonach die beschichteten Kügelchen abgetrennt, gewaschen und getrocknet werden.

13. Verfahren zum Erhalten des pharmazeutischen Präparats nach Anspruch 1, dadurch gekennzeichnet, daß die Lösung des gelierfähigen Hydrokolloids einem Medium zugesetzt wird, in dem Gelieren des Hydrokolloids erfolgt (Gelierlösung); die gebildeten Millikügelchen, Mikrokügelchen, Nanokügelchen oder Teilchen vom Array-Typ abgetrennt und in einer konzentrierten Lösung des Arzneimittels suspendiert werden, aus der das Arzneimittel in die Kügelchen eindiffundiert; wonach die Millikügelchen, Mikrokügelchen, Nanokügelchen oder Teilchen vom Array-Typ abgetrennt und in einer Lösung des kationischen Polysaccharids suspendiert werden, wo die Ablagerung des kationischen Polysaccharids auf der Oberfläche der Kügelchen erfolgt; wonach die beschichteten Kügelchen abgetrennt, gewaschen und getrocknet werden.

14. Pharmazeutisches Präparat nach einem der Ansprüche 1 bis 9, dadurch gekennzeichnet, daß gegebenenfalls - und insbesondere im Fall von Arzneimitteln, die gegenüber den chemischen/enzymatischen Bedingungen des Magens empfindlich sind - die Teilchen innerhalb von Gelatinekapseln mit einem enterischen Überzug, der die Teilchen schützt, bevor sie in den Zwölffingerdarm gelangen, verabreicht werden.

Revendications

1. Préparation pharmaceutique, caractérisée en ce qu'elle comprend de millisphères déshydratées, des microsphères déshydratées, des nanosphères déshydratées ou des particules déshydratées de type matrice, se composant d'un noyau d'un hydrocolloïde capable de former un gel sur lequel a été déposé un film d'un polysaccharide cationique, et à l'intérieur duquel un médicament pharmacologiquement utile a été incorpore.

2. Préparation pharmaceutique selon la revendication 1, caractérisée en ce que, facultativement, un promoteur d'absorption via les muqueuses a également été incorporé dans ledit noyau.

3. Préparation pharmaceutique selon les revendications 1 et 2, caractérisée en ce que les hydrocolloïdes capables de former un gel sont des polymères d'origine biologique ou synthétique qui sont solubles dans l'eau et qui peuvent former des gels solides par interaction avec les sels d'éléments métalliques (plus particulièrement les sels de métaux alcalino-terreux et plus particulièrement, les sels de sodium) ou par variations du pH de leurs solutions aqueuses ou par réticulation chimique.

4. Préparation pharmaceutique selon les revendications 1, 2 et 3, caractérisée en ce que les hydrocolloïdes capables de former un gel sont, de préférence, l'agar, la pectine, la gomme xanthane, la gomme guar, la gomme de caroube, l'acide hyaluronique, la caséine, les sels solubles dans l'eau de l'acide alginique (plus particulièrement, l'alginate de sodium), et leurs mélanges.

5. Préparation pharmaceutique selon les revendications 1 et 2, caractérisée en ce que les polysaccharides cationiques sont des sucres polyvalents naturels ayant des résidus qui peuvent supporter une charge positive et des sucres polyvalents naturels chimiquement fonctionnalisés avec des résidus qui peuvent supporter une charge positive, en particulier des sucres polyvalents aminés et leurs sels acides ; des dextranes fonctionnalisés avec des groupes amino primaires, secondaires, tertiaires et/ou quaternaires et leurs sels acides.

6. Préparation pharmaceutique selon les revendications 1, 2 et 5, caractérisée en ce que les polysaccharides cationiques sont, de préférence, le diéthylaminoéthyldextrane et le diméthylaminoéthyldextrane, leurs sels acides et leurs mélanges.

7. Préparation pharmaceutique selon les revendications 1 et 2, caractérisée en ce que les promoteurs d'absorption via les muqueuses sont des esters de choline, des agents chélatants, des salicylates, des phénothiazines, des carnitines d'acyle, des alpha-cétoaldéhydes, des tensioactifs, des collates, des lysolécithines et leurs mélanges.

8. Préparation pharmaceutique selon les revendications 1, 2 et 7, caractérisée en ce que les promoteurs d'absorption via les muqueuses sont, de préférence, la lysolécithine et les sels d'acides gras, notamment le caproate de sodium (hexanoate de sodium), le caprylate de sodium (octanoate de sodium), le caprate de sodium (décanoate de

sodium) et le laurate de sodium (dodécanoate de sodium).

9. Préparation pharmaceutique selon les revendications 1 et 2, caractérisée en ce que les médicaments incorporés sont :

- Des médicaments antibactériens tels que la gentamycine ; les quinolones comme la ciprofloxacine ; les pénicillines ou les céphalosporines ;
- Des agents antiviraux tels que la rifampicine ou l'acyclovir ;
- Des composés antifongiques tels que l'amphotérécine B, le myconazole, le terconazole, l'éconazole, l'isoconazole, le thioconazole, le biphonazole, le clotrinazole, le cétoconazole, le butaconazole, l'itraconazole, l'oxyconazole, le phenticonazole, la nystatine, le naphtyphène, le zinoconazole, la cyclopyroxolamine ou le fluconazole ;
- Des composés antiparasitaires tels que les dérivés de l'antimoine ;
- Des composés antitumoraux et antinéoplasiques tels que l'adriamycine, la vinblastine, la vincristine, la mitomycine C, la doxorubicine, la daunorubicine, le méthotrexate, la cisplatine et autres ;
- Des antimétabolites ;
- Des protéines telles que l'albumine ;
- Des toxines telles que la toxine diphtérique ;
- Des enzymes telles que la catalase ;
- Des peptides tels que l'hirudine, la somatostatine ou la timopentine ;
- Des hormones telles que les oestrogènes ;
- Des hormones peptidiques telles que l'hormone de croissance humaine, l'hormone de croissance porcine, l'hormone de croissance bovine, la calcitonine humaine, la calcitonine de saumon, la carbocalcitonine, l'insuline ou LHRH et leurs analogues ;
- Des antagonistes hormonaux ;
- Des neurotransmetteurs tels que l'acétylcholine ;
- Des antagonistes neurotransmetteurs ;
- Des glycoprotéines telles que l'acide hyaluronique ;
- Des lipoprotéines telles que l'alpha-lipoprotéine ;
- Des immunoglobulines telles que l'IgG ;
- Des immunomodulateurs tels que l'interféron ou l'interleukine ;
- Des immunosuppresseurs tels que la cyclosporine-A ;
- Des vasodilatateurs ;
- Des colorants tels que l'Arsénaze III ;
- Des marqueurs radioactifs tels que ^{14}C ;
- Des composés opaques aux radiations tels que ^{14}Te ;
- Des composés fluorescents tels que la carboxyfluorescéine ;
- Des récepteurs cellulaires tels que la protéine du récepteur d'oestrogènes ;
- Des agents anti-inflammatoires non stéroïdiens tels que l'indométhacine, l'ibuprofène, le sulindac, le diclofénac, le cétorolac et le naproxène ;
- Des agents anti-inflammatoires tels que la déxaméthasone ;
- Des antiglaucomateux tels que la pilocarpine ou le thymolol ;
- Des composés mydriatiques ;
- Des anesthésiques locaux tels que la lidocaïne ;
- Des narcotiques tels que la codéine ;
- Des vitamines telles que l'alpha-tocophérol ;
- Des acides nucléiques tels que la thymine ;
- Des polynucléotides tels que l'ARN ;
- Des composés psychoactifs ou anxiolytiques tels que le diazépam ;
- Des mono-, di- et polysaccharides tels que le glycogène ;
- Des glycosaminoglycanes tels que les héparines non fractionnées, les héparines de faible poids moléculaire, les pentasaccharides, le dermatane-sulfate et ses dérivés, l'héparane-sulfate et ses dérivés, le chondroïtine-4-sulfate ou le chondroïtine-6-sulfate et ses dérivés ;
- Des agents cardiovasculaires tels que les alpha-bloquants, les bêta-bloquants, les inhibiteurs de canaux calciques, les inhibiteurs ACE, les inhibiteurs des récepteurs H_2 de histamine, ou les inhibiteurs des récepteurs H3T de sérotonine ;
- Des prostaglandines.

10. Procédure permettant d'obtenir la préparation pharmaceutique selon la revendication 1, caractérisée en ce que le médicament est dissous, mis en suspension ou émulsionné dans une solution de l'hydrocolloïde capable de former un gel ; la solution, suspension ou émulsion résultante est ajoutée à un milieu dans lequel la gélification de l'hydrocolloïde se produit (solution de gélification) ; les millisphères, microsphères, nanosphères ou particules de type matrice qui sont formées sont séparées et mises en suspension dans une solution du polysaccharide cationique où le dépôt du polysaccharide cationique sur la surface des sphères se produit, après quoi les sphères recouvertes sont séparées, lavées et séchées.

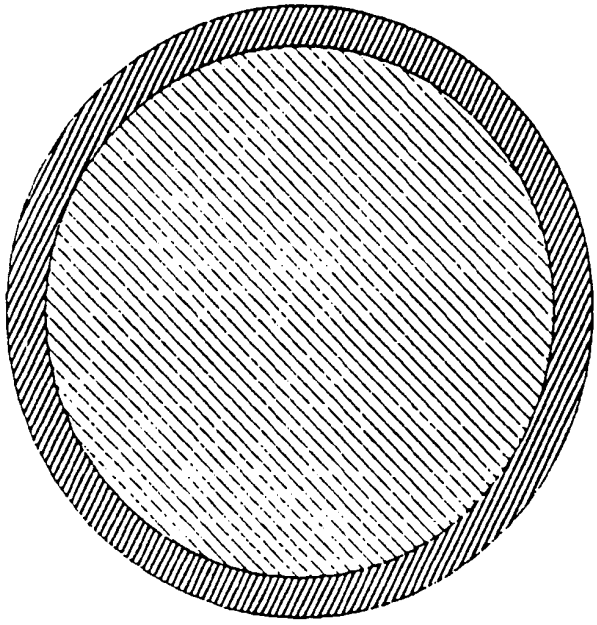
11. Procédure permettant d'obtenir la préparation pharmaceutique selon les revendications 1 et 2, caractérisée en ce que le médicament et le promoteur d'absorption sont dissous, mis en suspension ou émulsionnés dans une solution de l'hydrocolloïde capable de former un gel ; la solution, suspension ou émulsion résultante est ajoutée à un milieu dans lequel la gélification de l'hydrocolloïde se produit (solution de gélification) ; les millisphères, microsphères, nanosphères ou particules de type matrice qui sont formées sont séparées et mises en suspension dans une solution du polysaccharide cationique où le dépôt du polysaccharide cationique sur la surface des sphères se produit, après quoi les sphères recouvertes sont séparées, lavées et séchées.

12. Procédure permettant d'obtenir la préparation pharmaceutique selon la revendication 1, caractérisée en ce que le promoteur d'absorption est dissous, mis en suspension ou émulsionné dans une solution de l'hydrocolloïde capable de former un gel ; la solution, suspension ou émulsion résultante est ajoutée à un milieu dans lequel la gélification de l'hydrocolloïde se produit (solution de gélification) ; les millisphères, microsphères, nanosphères ou particules de type matrice qui sont formées sont séparées et mises en suspension dans une solution concentrée du médicament à partir de laquelle le médicament se diffuse à l'intérieur des sphères ; puis les millisphères, microsphères, nanosphères ou particules de type matrice sont séparées et mises en suspension dans une solution du polysaccharide cationique où le dépôt du polysaccharide cationique sur la surface des sphères se produit, après quoi les sphères recouvertes sont séparées, lavées et séchées.

13. Procédure permettant d'obtenir la préparation pharmaceutique selon la revendication 1, caractérisée en ce que la solution de l'hydrocolloïde capable de former un gel est ajoutée à un milieu dans lequel la gélification de l'hydrocolloïde se produit (solution de gélification) ; les millisphères, microsphères, nanosphères ou particules de type matrice qui sont formées sont séparées et mises en suspension dans une solution concentrée du médicament à partir de laquelle le médicament se diffuse à l'intérieur des sphères ; puis les millisphères, microsphères, nanosphères ou particules de type matrice sont séparées et mises en suspension dans une solution du polysaccharide cationique où le dépôt du polysaccharide cationique sur la surface des sphères se produit, après quoi les sphères recouvertes sont séparées, lavées et séchées.

14. Préparation pharmaceutique selon les revendications 1 à 9, caractérisée en ce que, facultativement, et notamment dans le cas de médicaments qui sont sensibles aux conditions chimiques/enzymatiques de l'estomac, lesdites particules sont administrées à l'intérieur de capsules de gélatine à délitage entérique qui protègent les particules jusqu'à ce qu'elles pénètrent dans le duodénum.

FIG. 1



MATRIX

COATING

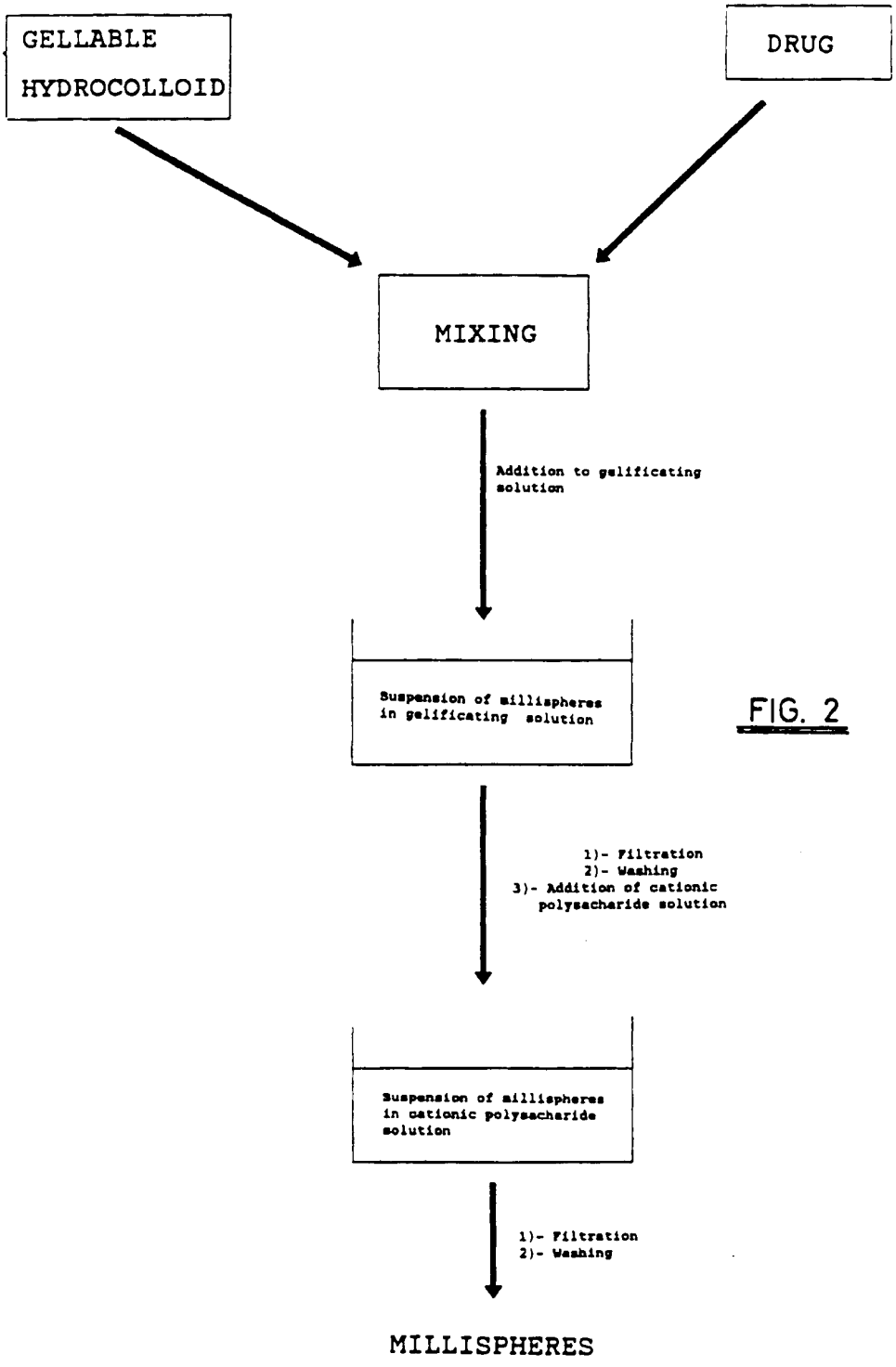

GELLABLE HYDROCOLLOID
DRUG
MIXING
Addition to gelificating solution
Suspension of millispheres in gelificating solution
1)- Filtration
2)- Washing
3)- Addition of cationic polysaccharide solution
Suspension of millispheres in cationic polysaccharide solution
1)- Filtration
2)- Washing
MILLISPHERES

FIG. 2

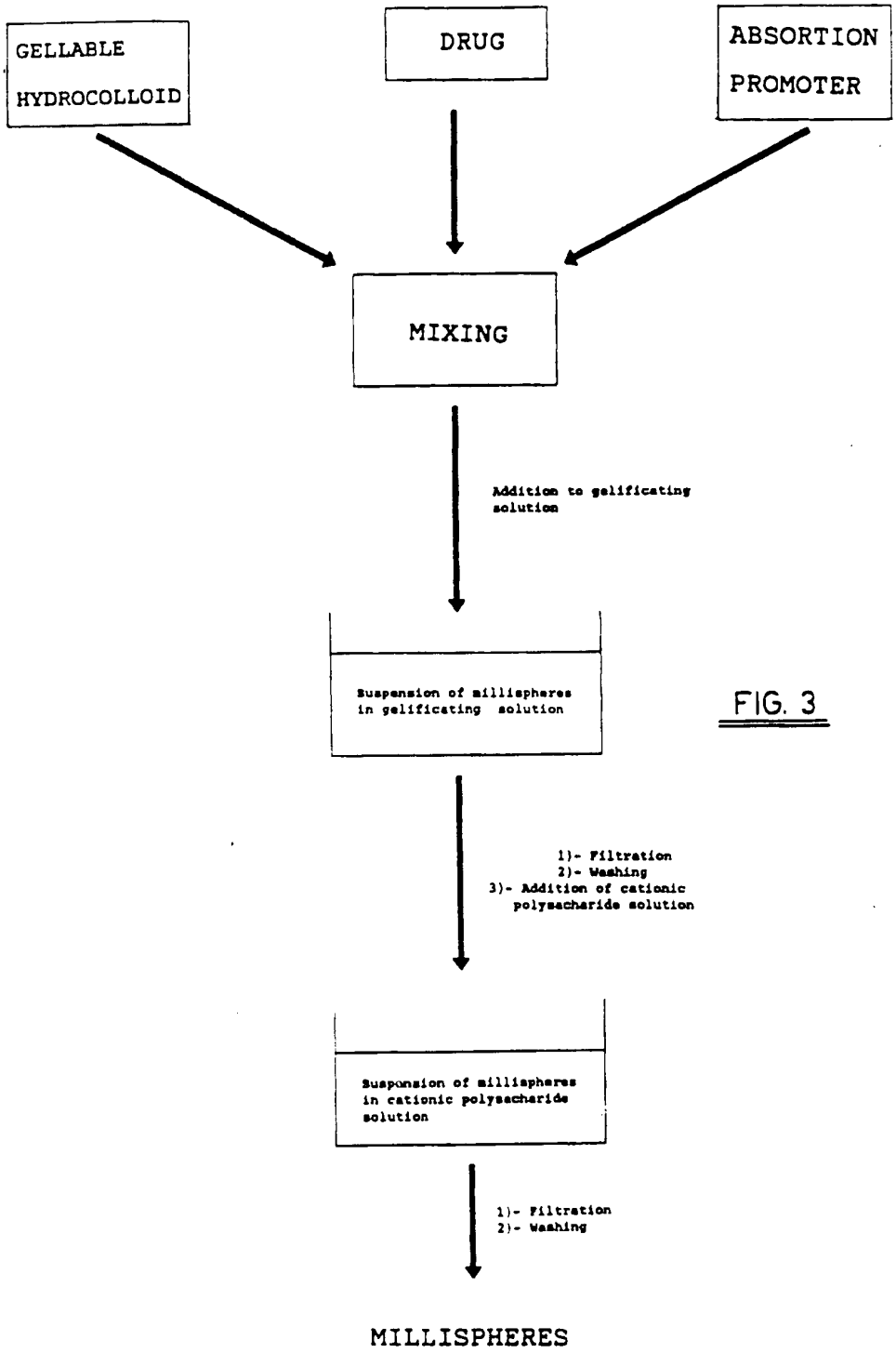

GELLABLE HYDROCOLLOID
DRUG
ABSORTION PROMOTER
MIXING
Addition to gelificating solution
Suspension of millispheres in gelificating solution
1)- Filtration
2)- Washing
3)- Addition of cationic polysaccharide solution
Suspension of millispheres in cationic polysaccharide solution
1)- Filtration
2)- Washing
MILLISPHERES

FIG. 3

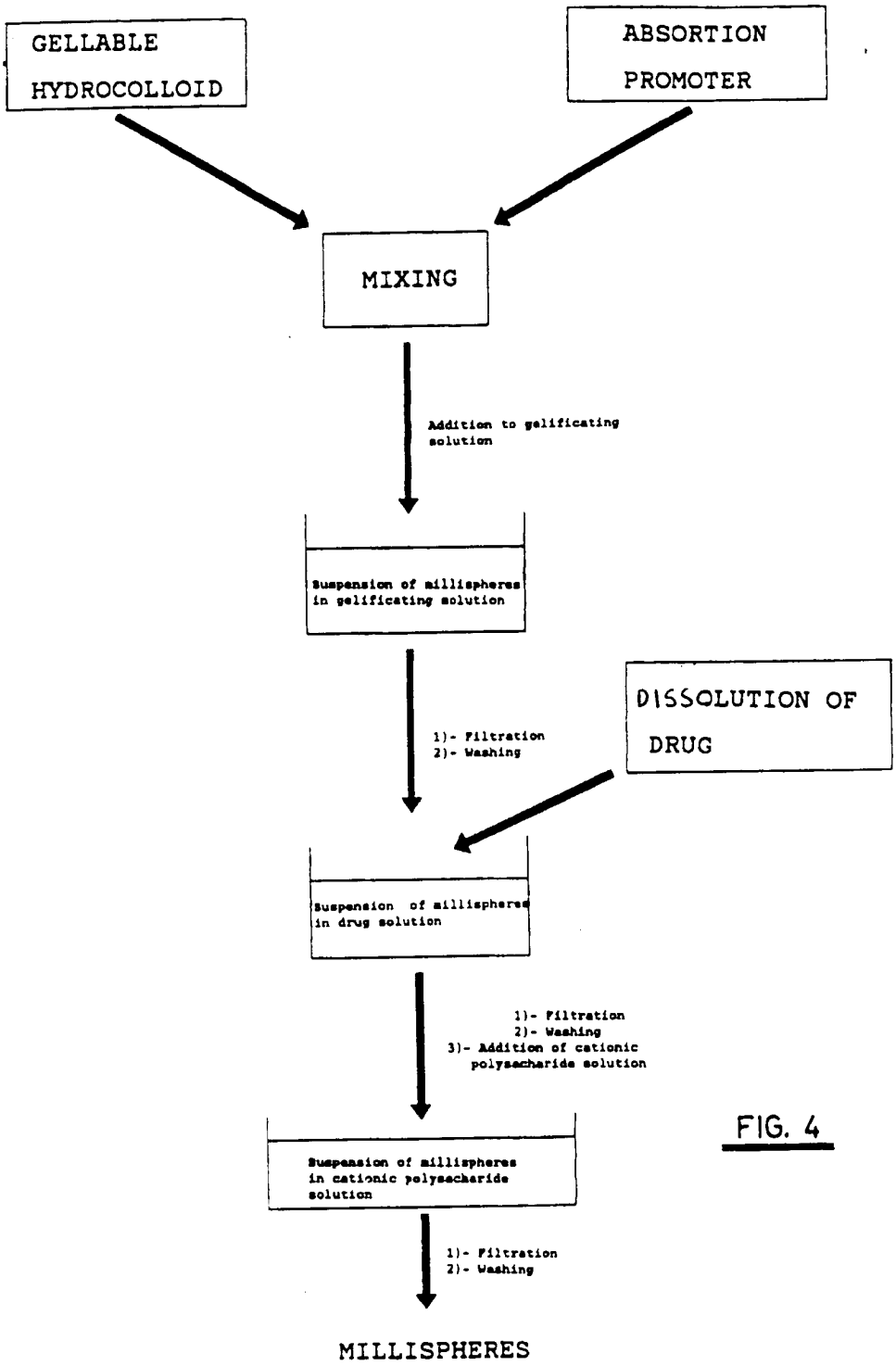

GELLABLE HYDROCOLLOID
ABSORTION PROMOTER
MIXING
Addition to gelificating solution
Suspension of millispheres in gelificating solution
1)- Filtration
2)- Washing
DISSOLUTION OF DRUG
Suspension of millispheres in drug solution
1)- Filtration
2)- Washing
3)- Addition of cationic polysaccharide solution
Suspension of millispheres in cationic polysaccharide solution
1)- Filtration
2)- Washing
MILLISPHERES

FIG. 4

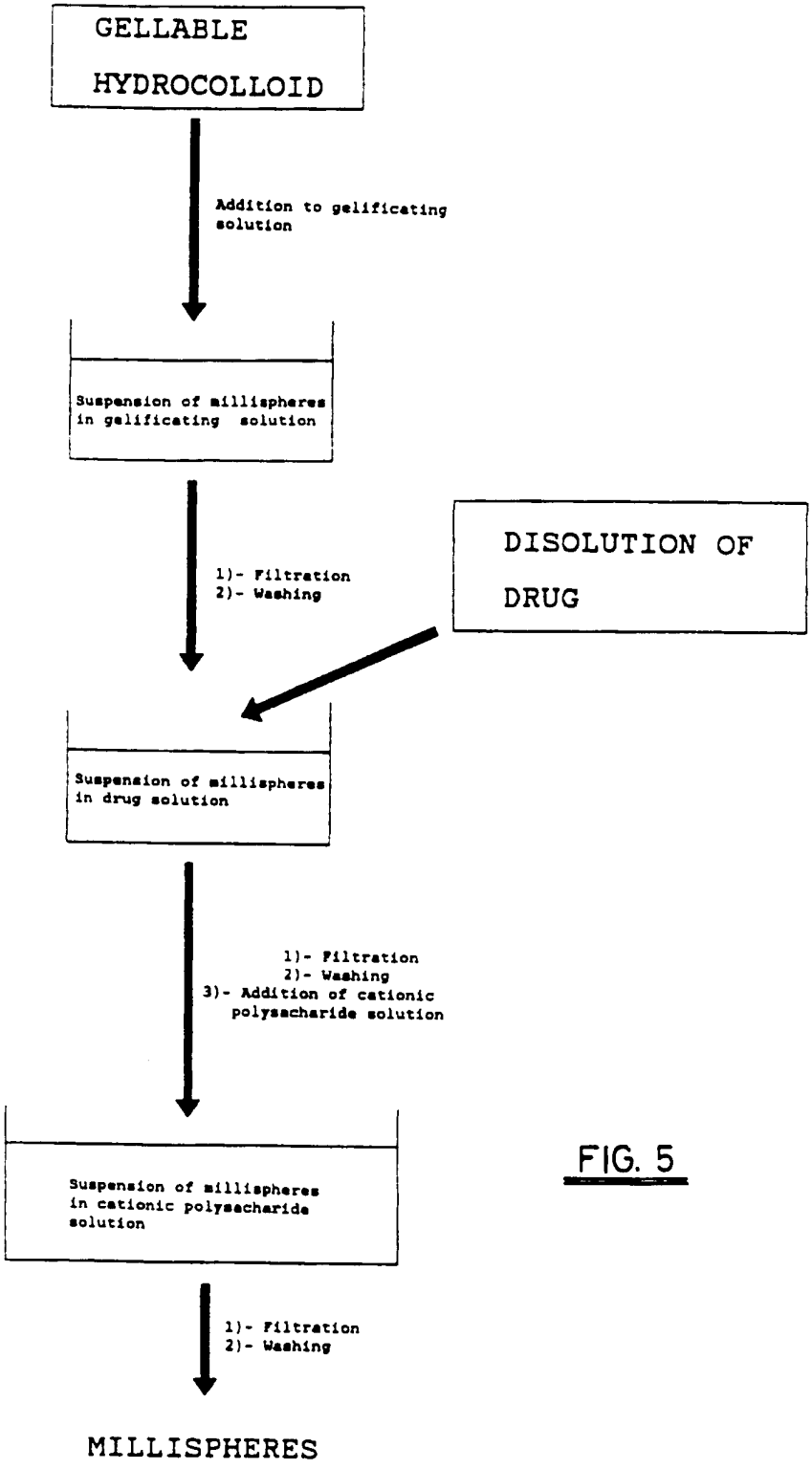

GELLABLE HYDROCOLLOID
Addition to gelificating solution
Suspension of millispheres in gelificating solution
1)- Filtration
2)- Washing
DISOLUTION OF DRUG
Suspension of millispheres in drug solution
1)- Filtration
2)- Washing
3)- Addition of cationic polysaccharide solution
Suspension of millispheres in cationic polysacharide solution
1)- Filtration
2)- Washing
MILLISPHERES

FIG. 5